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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,687	06/13/2006	Pasqua Anna Oreste	GRT/3687-177	2203

23117 7590 11/24/2009
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EXAMINER

BLAND, LAYLA D

ART UNIT	PAPER NUMBER
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1623

MAIL DATE	DELIVERY MODE
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11/24/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/582,687	Applicant(s) ORESTE ET AL.	
	Examiner LAYLA BLAND	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 1-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-21, 23-25 and 27 is/are rejected.
- 7) ☐ Claim(s) 22 and 26 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/24/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

This Office Action is in response to Applicant's request for continued examination (RCE) filed September 24, 2009, and amendment and response to the Final Office Action (mailed March 19, 2009), filed September 24, 2009 wherein claims 1 and 17 are amended. Applicant's declaration of Pasqua Oreste submitted September 24, 2009 under 37 CFR 1.132, is acknowledged and will be further discussed below.

Claims 1-27 are pending.

Claims 1-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 17-27 are examined on the merits herein.

It is noted that Applicant requests a telephone interview to discuss outstanding issues if the claims are not allowed. The examiner placed a call to Mr. Tanigawa on November 18, 2009, inviting him to return the call and discuss the issues.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

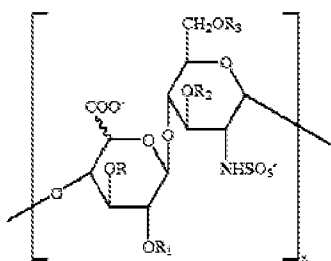
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oreste et al. (WO 02/50125, June 27, 2002, PTO-1449 submitted June 13, 2006) as evidenced by Jacobsson et al. (Biochemical Journal, 1979, 179, pp. 77-87).

Oreste teaches glycosaminoglycans derived from K5 polysaccharides [see abstract] which consist of a mixture of chains in which at least 90% of said chains have the formula

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, wherein 40-60% of the uronic acid units are iduronic acid, the sulfation degree is 2.3 to 2.9, R_3 is 85% to 95% SO_3^- , R_2 is 17-21% SO_3^- , R_1 is about 15-35% SO_3^- in iduronic units and 0-5% SO_3^- in glucuronic units, R is from 20-40% SO_3^- in glucuronic units and 0-5% in iduronic units, and the mean molecular weight is from about 6,000 to about 8,000 [claims 25 and 31]. In one embodiment, n is from 3 to 15 [claim 29]. Oreste also teaches pharmaceutical compositions comprising these compounds and pharmaceutically acceptable carriers [claim 38].

The low molecular weight product is obtained by chemical depolymerization at the end of one of steps (ii)-(vi) [page 14, lines 27-31]. Depolymerization can be carried out by nitrous acid and sodium borohydride [page 15, lines 7-14]. Step (iii), oversulfation, is carried out by converting the C5 epimerised N-sulfate K5 into a tertiary or quaternary salt thereof and then treating the salt with an O-sulfating agent [page 12, lines 15-18]. The conversion to a salt is done by bringing an acidic solution of the product from step (ii) to neutrality with tetrabutylammonium hydroxide [page 28, lines 30-31].

Oreste exemplifies a process wherein chemical depolymerization is carried out at the end of the synthesis (after step vi) and is silent on the structure at the reducing end of the majority of the chains. However, the skilled artisan would understand that

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compounds made by Oreste's methods, wherein the compounds are depolymerized after step (ii) via nitrous acid depolymerization and reaction with sodium borohydride [page 14, lines 27-31 and page 15, lines 1-6] would have the claimed structure at the reducing end of the majority of the chains. Jacobsson teaches that chemical depolymerization of heparin-like polysaccharides with nitrous acid and reduction with sodium borohydride generates 2,5-anhydromannitol at the reducing end [page 73, left column, lines 14-30]. Thus, the skilled artisan would expect that chemical depolymerization of Oreste's step (ii) product (which is analogous to the claimed starting material) would contain 2,5-anhydromannitol at the reducing end of the resulting chains. Oreste's compounds generated after step (ii) are further subjected to oversulfation conditions (step iii) and further O-sulfating agents (step v), so the structure at the reducing end would also be sulfated in the majority of the chains. Thus, if the skilled artisan followed Oreste's suggestion to carry out nitrous acid depolymerization at the end of step (ii), the skilled artisan would expect that the claimed product would result.

Claim 17 is a product-by process claim. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up

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containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

The limitation "depolymerized" is also interpreted as drawn to the method of production, which results in a low molecular weight product.

Response to Arguments

Applicant argues that sulfation of glucosamine units, particularly glucosamine-3-O-sulfate groups, is required for the activity of the claimed compounds, and that the activity of those compounds is unexpected. This argument has been carefully considered but is not persuasive. See MPEP 716.02(d): Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support," and MPEP 716.02(b): "evidence of secondary considerations must be relevant to the subject matter as claimed." In other words, the showing the unexpected results must be reviewed to see if the results occur over the entire claimed range, and there should be a connection between the objective evidence of nonobviousness and the claimed invention. Applicant's response and the declaration of Pasqua Oreste indicate that glucosamine-3-O-sulfate groups are critical for the unexpected properties of the composition. Claims 17-21, 23-25, and 27 are not limited with respect to glucosamine-3-O-sulfate groups and thus are not commensurate in scope with the unexpected properties argued by Applicant and do not share a nexus with the unexpected properties argued by Applicant. Claims 22 and 26, which are limited with respect to glucosamine-3-O-sulfate groups,

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were previously indicated as allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant argues that treating the LMW-epiK5-N-sulfate with base for 30-60 minutes before oversulfation produces the spectacular result of introducing a large number of sulfate groups onto the otherwise resistant 3-OH group of glucosamine subunits. This argument is not persuasive because there is no explanation or evidence to support the argument. The prior art is silent with respect to the time frame of converting the epiK5-N-sulfate to a salt. The prior art process also differs from Example 1 and the example given in the Oreste declaration in that the prior art oversulfation reaction appears to be much more concentrated than the instant examples, and the prior art does not disclose equivalents of reagents used. Thus, it is impossible to make a direct comparison with respect to the undisclosed time frame for forming a salt in the prior art and the claimed 30-60 minutes. Furthermore, the prior art process and the instant process comprise multiple steps, any of which could affect the structure of the final product. The Oreste declaration appears to be directed towards establishing the importance of 3-O-glucosamine sulfate groups for the activity of the composition, but the examiner was unable to locate any data pertaining to the importance of 30-60 minutes for salt formation. Note that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The burden is shifted to Applicant to show factually supported objective evidence to rebut the prima facie case of obviousness over the prior art. It is

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also noted that only claim 17 requires the treatment for 30-60 minutes. Claims 18-21, 23-25, and 27 do not require treatment for 30-60 minutes.

For these reasons, the rejection is maintained.

Conclusion

Claims 22 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623